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Bruce S. Londa

#19
Amdt
1/19/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney's Docket No.: 101195-18

Examiner	:	A. Chakrabarti
Group Art Unit	:	1655
Serial No.	:	09/454,740
Filed	:	December 6, 1999
Applicant(s)	:	Timo Hillebrand
For	:	Formulations and method for isolating nucleic acids from optional complex starting materials and subsequent complex gene analysis

AMENDMENT
AND REQUEST FOR EXTENSION OF TIME

Hon. Commissioner of Patents
Washington, D.C. 20231

Sir:

In the claims

Please amend claim 1 as follows:

1. (twice amended) A kit for isolating nucleic acids from complex starting materials in the absence of chaotropic components by binding nucleic acid to a substrate, the kit comprising

a lysis/buffer system consisting essentially of

at least one antichaotropic salt component,

a substrate means for binding DNA,

a wash buffer comprising at least 50% ethanol, and

a low salt elution buffer, and

optionally one or more detergent or additive chosen from the group consisting of tris-HCl, EDTA, polyvinyl pyrolidone, CTAB, triton X-100, n-lauryl sarcosine, sodium citrate, DTT, SDS, and Tween;

optionally enzymes; and

optionally an alcohol for binding to the substrate means.

Remarks

This is in response to an Official Action dated June 6, 2001. Reconsideration in view of the following is respectfully submitted.

A petition for a three month extension of the term is attached. The undersigned also encloses a Change of Address of Firm. Please forward all future correspondence to the address indicated therein.

Claim 1 has been amended to emphasize that the lysis/buffer system does not contain phenol/chloroform. Support is found in the specification, wherein phenol/chloroform is used to isolate nucleic acids under the 'classical methods' (i.e. prior art) approach. See page 1, lines 34-38 in specification. In view of the remaining disclosure and the attachment, it is clear inherent that the instant invention does not employ, and in fact teaches away from using phenol/chloroform.

In order to include this limitation, claim 1 is amended to have the transitional language 'consisting essentially of'. Support for this change is found in the specification at page 1, lines 34-38. The term 'consisting essentially of' limits the scope of the claim to the specified materials and those that do not materially affect the basic and novel characteristics of the claimed invention. *See In re Herz*, 190 U.S.P.Q. 461, 463 (CCPA 1976); *See also* MPEP §2111.03. From the teaching of Anderson, below, it is clear that the presence of phenol/chloroform is a material aspect of that prior art method, and would therefore be outside of the scope of the amended claim.

The Examiner rejects claims 1-5, 7, 9, and 28-29 under 35 U.S.C. 103(a) in view of Anderson, Cleuziat, Nochumson, and Gonsalves. Anderson teaches an isolated cDNA that encodes TIA-1 binding proteins. Cleuziat discloses a method for amplifying nucleic acid sequences by strand displacement using DNA/RNA chimeric primers. Nochumson teaches a method for separating and recovering desired biological substances from liquids containing such substances. Gonsalves teaches a DNA molecule that encodes for a protein or polypeptide coat of a grapevine leafroll virus. As to the rejection based upon Anderson and Cleuziat, it is inaccurate to combine the two references to obtain the instant invention because both references are directed toward two different types of goals. While Anderson is directed toward the isolation of a target nucleic acid, Cleuziat addresses the *amplification* of *the* target nucleic acid. Cleuziat must be performed subsequent to that method taught in Anderson, wherein the sequences must initially be isolated in order to find the targeted sequences. See Cleuziat, col. 8, lines 6-66. It is not obvious to someone reasonably skilled in the art to combine two references that address two different goals.

Furthermore, ***Anderson also requires the use of phenol, chloroform and alcohol to isolate DNA***. See col. 15, lines 25-6.

In contrast, the instant invention does not employ the aforementioned chemicals for binding DNA, and in fact excludes them according to amended claim 1. Thus, even if someone reasonably skilled in the art combined Anderson and Cleuziat, that individual would necessarily use a solid substrate in combination with the phenol, chloroform and alcohol to isolate the DNA. Therefore, it is surprising that, when using a solid substrate in the absence of the phenol, chloroform, and alcohol to isolate DNA based upon the prior art technique, the claimed kit is nevertheless superior. See attached Rule 132 Declaration. Therefore, the claims are not obvious in view of the cited combination of references.

As to the Nochumson reference, Nochumson discloses *chaotropic* salts for binding to nucleic acids. See col. 12, lines 14-15. Chaotropic salts are characterized by denaturing proteins, increasing the solubility of non-polar substances in water and destroying hydrophobic interactions. However, the instant invention discloses *antichaotropic* salts to bind the DNA. In addition, the antichaotropic salts show a surprising result in their effectiveness to bind DNA. See e.g., Figs. 4 and 5 in the specification. Moreover, the buffer in Nochumson keeps the DNA bound to the solid substrate. See col. 12, lines 34-37. In contrast, the buffer in the instant invention elutes

the DNA away from the solid substrate. See specification at page 6, lines 25-30. Thus, a combination of the aforementioned references would lead to an inaccurate representation of the instant invention, because the prior art does not contemplate the antichaotropic elements disclosed in the instant invention to bind DNA.

Gonsalves teaches a DNA molecule that encodes for a protein or polypeptide coat of a grapevine leafroll virus. It is improper to combine the references to obtain the instant invention, because the effect of using proteinase K is unknown in the presence of a buffer having *antichaotropic* components. Applicant has surprisingly found that the antichaotropic buffer solution mediates the binding of DNA, and stabilizes the protein and enzymes acting proteolytically. In contrast, a chaotropic buffer in the presence of the nucleic acid and the proteolytic enzymes in the starting material would be expected to denature the enzymes, thereby destroying their utility.

The examiner further rejected claims 1-5, 7-9, and 28-29 under 35 U.S.C. 103(a) in view of Anderson, Cleuziat, Nochumson, Gonsalves and Summerton references. Anderson, Cleuziat, Nochumson, Gonsalves were described earlier. Summerton discloses compositions and methods for detecting and isolating

nucleic acid sequences. Summerton is an inaccurate reference in this case. Summerton uses pH not as a technique to make a stable storage reaction vessel, but rather the reference uses pH to disrupt the DNA complex (col. 10, lines 38-9). Summerton states that the "addition of alkali to give a pH of 12 or above rapidly disrupts DNA duplexes". The reference does not contemplate the use of pH as a technique to create a stable reaction vessel. Therefore, it would not be obvious to someone skilled in the art to combine these two references, and the claims are not rendered obvious.

The examiner further objected to claims 1-5, 7, 9-11, and 28-29 as being obvious in view of Anderson, Cleuziat, Nochumson, Gonsalves and Woodard references. Anderson, Cleuziat, Nochumson, Gonsalves were described earlier. Woodard discloses a glass fiber membrane that can bind DNA, and then allow elution of DNA from the membrane. Anderson does not describe a means for binding DNA. Rather, glass beads are provided as a physical decomposition agent that does <u>not</u> participate in the binding of DNA. If Woodard is combined with the aforementioned references, a person skilled in the art could safely assume that the glass membrane is used in the same manner as the glass beads- not as a substrate means for binding the nucleic acid, but as a physical agent for grinding the starting material. In the instant

claims, the glass membrane or substrate binds to the nucleic acid, and is partially responsible for the resolution and quality of the nucleic acid obtained in the invention. Thus, a combination of the two references would lead to an illogical and unpredictable result. The claims are not rendered obvious.

The examiner rejects claims 1-5, 7, 9, 26, and 28-29 under 35 U.S.C. 103(a) as being obvious in view of Anderson, Cleuziat, Nochumson, Gonsalves and Asgari references. Anderson, Cleuziat, Nochumson, Gonsalves were described above. Asgari describes a method of identifying a fetal red blood cell based on the presence of RNA in fetal hemoglobin. Asgari does not provide enough guidance as to the use of ammonium chloride in a lysis/buffer system. While the aforementioned references disclose a buffer solution, Asgari does not describe the ammonium chloride in the context of a buffer system, but rather as a lysing agent. There is no evidence to support the reasonable combination of the references, since the examples in Asgari do not even mention the use of ammonium chloride. There is not enough guidance in Asgari to support the combination. Moreover, neither of the references cites ammonium chloride as an antichaotropic agent. Thus, the claims are not rendered obvious in view of the references.

Wherefore, allowance of all pending claims is earnestly solicited.

Respectfully submitted,

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1. (twice amended) A kit for isolating nucleic acids from complex starting materials in the absence of chaotropic components by binding nucleic acid to a substrate, the kit comprising

a lysis/buffer system [comprising] consisting essentially of

at least one antichaotropic salt component [and enzymes],

a substrate means for binding DNA,

a wash buffer comprising at least 50% ethanol, and

a low salt elution buffer, and

optionally one or more detergent or additive chosen from the group consisting of tris-HCl, EDTA, polyvinyl pyrolidone, CTAB, triton X-100, n-lauryl sarcosine, sodium citrate, DTT, SDS, and Tween;

optionally enzymes; and

optionally an alcohol for binding to the substrate means.